#33 In-Part

PATENT
Customer Number 22,852
Attorney Docket No. 1147-0142

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of: U.S. Patent No. 5,750,338	)	
Mark L. Collins et al.	)	Group Art Unit: 1655
Reissue Serial No.: 09/533,906 ✓	)	Examiner: D. Johannsen
Reissue Application Filed: March 8, 2000	)	
For: TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS	)	

REISSUE LITIGATION BOX
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

AMENDMENT

In response to the Office Action mailed February 12, 2002, please amend this application as follows:

IN THE PATENT

Delete the Related U.S. Application Data [62] in its entirety and replace with:

--Divisional of Ser. No. 124,826, Sept. 21, 1993, abandoned, which is a continuation of Ser. No. 946,749, Sept. 17, 1992, abandoned, which is a continuation of Ser. No. 648,468, Jan. 31, 1991, abandoned, which is a continuation-in-part of Ser. No. 644,967, Jan. 22, 1991,

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abandoned, which is a continuation of Ser. No. 136,920, Dec. 21, 1987, abandoned, which is a continuation-in-part of Ser. No. 922,155, Oct. 23, 1986.--

Column 1, lines 4 through 18, amend the text as follows:

--This application [is a Reissue of Ser. No. 238,080, filed May 3, 1994, now U.S. Patent No. 5,750,338, which] is a divisional [continuation] of application Ser. No. 124,826, filed Sept. 21, 1993, now abandoned, which is a continuation of application Ser. No. 946,749, filed Sept. 17, 1992, now abandoned, which is a continuation of application Ser. No. 648,468, filed Jan. 31, 1991, now abandoned, which is a continuation-in-part of application Ser. No. 644,967, filed Jan. 22, 1991, now abandoned, which is a continuation of application Ser. No. 136,920, filed Dec. 21, 1987, now abandoned and hereby incorporated by reference, which application is a continuation-in-part of application Ser. No. 922,155, filed Oct. 23, 1986, now abandoned and hereby incorporated by reference.--

IN THE CLAIMS

Please cancel claims 41, ~~and~~ 47, and 53-63 without prejudice.

Please amend claims 1, 5, 7, 11, 13, 14, 16, 19, 20-22, 24-28, 30, 34-36, and 38 as follows:

1. (Amended) A method for amplifying a target polynucleotide contained in a sample comprising the steps of:

(a) contacting the sample with a first support which binds to the target polynucleotide;

(b) substantially separating the support and bound target polynucleotide from the sample; and

(c) amplifying *in vitro* the separated target polynucleotide.

5. (Amended) The method of claim **4** wherein the polymerase is a DNA polymerase, an RNA polymerase, or a transcriptase [or Qβ replicase].

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7. (Amended) A method for detecting a target polynucleotide contained in a sample comprising the steps of:

(a) contacting the sample with a first support which binds to the target polynucleotide;

(b) substantially separating the first support and bound target polynucleotide from the sample;

(c) amplifying *in vitro* the separated target polynucleotide; and

(d) detecting the presence of the amplified target polynucleotide as indicative of the presence of the target polynucleotide in said sample.

11. (Amended) The method of claim **10** wherein the polymerase is a DNA polymerase, an RNA polymerase, or a transcriptase [or Qβ replicase].

13. (Amended) The method of claim **7** wherein the amplified target polynucleotide is contacted with a label, and the presence of the target polynucleotide in the sample is indicated by detection of said label.

14. (Amended) The method of claim **7** wherein the amplified target polynucleotide is contacted with a labeled probe, and the presence of the target polynucleotide in the sample is indicated by detection of said labeled probe.

16. (Amended) The method of claim **15** wherein the [amplified target polynucleotide is contacted with] second support includes a labeled probe, and the presence of the target polynucleotide in the sample is indicated by detection of said labeled probe.

19. (Twice amended) A method for detecting a target polynucleotide contained in a sample comprising the steps of:

(a) contacting the sample with a first support which binds to the target polynucleotide;

(b) substantially separating the first support and bound target polynucleotide from the sample;

(c) amplifying *in vitro* the [sample] separated target polynucleotide with a DNA polymerase;

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(d) contacting the amplified target polynucleotide with a second support which binds to the amplified target polynucleotide and also with a labeled probe which binds to the amplified target polynucleotide; and

(e) detecting the presence of the [amplified target polynucleotide] labeled probe as indicative of the presence of the target polynucleotide in said sample.

20. (Amended) A kit for detecting a target polynucleotide contained in a sample comprising:

(a) means for substantially separating the target polynucleotide from the sample prior to amplification of the target polynucleotide;

(b) means for amplifying *in vitro* the separated target polynucleotide;

(c) means for binding the amplified target polynucleotide to a solid support; and

(d) means for labeling the amplified target polynucleotide.

21. (Amended) The kit of claim **20** wherein:

(a) the means for substantially separating the target polynucleotide from the sample include a first support;

(b) the means for amplifying *in vitro* the separated target polynucleotide include a polymerase;

(c) the means for binding [that] the amplified target polynucleotide to a solid support include a capture probe which binds to the solid support and to the amplified target polynucleotide; and

(d) [a detector probe] the means for labeling the amplified target polynucleotide include a detector probe.

22. (Amended) The kit of claim **21** further comprising a [capture] probe which binds to the first support and to the target polynucleotide.

24. (Amended) A kit for amplifying a target polynucleotide contained in a sample comprising:

(a) means for substantially separating the target polynucleotide from the sample prior to amplification of the target polynucleotide; and

(b) means for amplifying *in vitro* the separated target polynucleotide.

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25. (Amended) The kit of claim **24** wherein:

(a) the means for substantially separating the target polynucleotide from the sample [includes] include a support which binds to the target polynucleotide; and

(b) the means for amplifying *in vitro* the separated target polynucleotide [includes] include a polymerase.

26. (Amended) The kit of claim **25** wherein:

(a) the polymerase is a DNA polymerase; and

(b) the means for substantially separating the target polynucleotide from the sample [includes] include a probe which binds to the target polynucleotide and the support.

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27. (Amended) A method for amplifying a target polynucleotide contained in a sample medium comprising the steps of:

(a) contacting the sample medium with reagent comprising a first nucleic acid probe which binds to the target polynucleotide to form a probe-target complex;

(b) contacting the sample medium with a support which binds to the first nucleic acid probe of the probe-target complex;

(c) substantially separating the support and bound probe target complex from the sample medium;

(d) contacting the support and bound probe-target complex with a second medium;

(e) releasing the probe-target complex into the second medium;

(f) substantially separating the support from the second medium; and

(g) amplifying *in vitro* the target polynucleotide present in the second medium.

28. (Amended) A method for detecting a target polynucleotide contained in a sample medium comprising the steps of:

(a) contacting the sample medium with reagent comprising a first nucleic acid probe which binds to the target polynucleotide to form a probe-target complex;

(b) contacting the sample medium with a support which binds to the first nucleic acid probe of the probe-target complex;

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(c) substantially separating the support and bound probe-target complex from the sample medium;

(d) contacting the support and bound probe-target complex with a second medium;

(e) releasing the probe-target complex into the second medium;

(f) substantially separating the support from the second medium;

(g) amplifying *in vitro* the target polynucleotide present in the second medium; and

(h) detecting the presence of the target polynucleotide in the second medium as indicative of the presence of the target polynucleotide in said sample.

30. (Amended) The method for detecting a target polynucleotide of claim **29** wherein the polymerase is a DNA polymerase, an RNA polymerase, or a transcriptase[, or Qβ replicase].

34. (Amended) A method for amplifying a target polynucleotide contained in a sample medium comprising the steps of:

(a) contacting the sample medium with a support and a probe which binds to the target polynucleotide and the support;

(b) substantially separating the support and bound probe and target polynucleotide from the sample medium;

(c) contacting the support and bound probe and target polynucleotide with a second medium;

(d) releasing the target polynucleotide into the second medium;

(e) substantially separating the support and bound probe from the second medium;

(f) amplifying *in vitro* the target polynucleotide present in the second medium.

35. (Amended) The method for amplifying a target polynucleotide of claim **34** wherein the target polynucleotide is amplified with a polymerase.

36. (Amended) The method for amplifying a target polynucleotide of claim **35** wherein the polymerase is a DNA polymerase, an RNA polymerase, or a transcriptase [or Qβ replicase].

38. (Amended) A method for detecting a target polynucleotide contained in a sample medium comprising the steps of:

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(a) contacting the sample medium with a support and probe which binds to the target polynucleotide and the support;

(b) substantially separating the support and bound probe and target polynucleotide from the sample medium;

(c) contacting the support and bound probe and target polynucleotide with a second medium;

(d) releasing the target polynucleotide into the second medium;

(e) substantially separating the support and bound probe form the second medium;

(f) amplifying *in vitro* the target polynucleotide present in the second medium; and

(g) detecting the presence of the amplified target polynucleotide in the second medium as indicative of the presence of the target polynucleotide in said sample.

Please amend claims 42, 44, 46, 48, 50, and 52 (which had been introduced in the Preliminary Amendment and which differ from those claims as set forth on the attached appendix) as follows:

42. (Amended) The amplification method of claim 1 wherein the amplification is linear or exponential.

44. (Amended) The amplification method of claim 1 wherein the target polynucleotide is amplified with a polymerase and at least one oligonucleotide primer.

46. (Amended) The amplification method of claim 1 wherein the target polynucleotide is amplified with more than one polymerase.

48. (Amended) The detection method of claim 7 wherein the amplification is linear or exponential.

50. (Amended) The detection method of claim 7 wherein the target polynucleotide is amplified with a polymerase and at least one oligonucleotide primer.

52. (Amended) The detection method of claim 7 wherein the target polynucleotide is amplified with more than one polymerase.

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Please add new claims 64-82 as follows:

64. The method of claim **1** wherein the separated target polynucleotide is amplified non-specifically with random primers.

65. The method of claim **1** wherein the separated target polynucleotide is amplified specifically with specially tailored primers.

66. The method of claim **7** wherein the separated target polynucleotide is amplified non-specifically with random primers.

67. The method of claim **7** wherein the separated target polynucleotide is amplified specifically with specially tailored primers.

68. The amplification kit of claim **25** wherein the means for amplifying the separated target polynucleotide include means for amplifying the target polynucleotide non-specifically with random primers.

69. The amplification kit of claim **25** wherein the means for amplifying the separated target polynucleotide include means for amplifying the target polynucleotide specifically with specially tailored primers.

70. The method of claim **9** wherein the probe first binds with the target polynucleotide by hybridizing to a specific sequence in the target polynucleotide, and then binds to the first support.

71. The method of claim **70** wherein the separated target polynucleotide is amplified non-specifically with random primers.

72. The method of claim **70** wherein the separated target polynucleotide is amplified specifically with specially tailored primers.

73. The method of claim **72** wherein the sample is a clinical sample.

74. The method of claim **73** wherein the probe comprises a nucleotide sequence specific to a complementary nucleotide sequence in the target polynucleotide and a homopolymeric tail sequence.

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60 75. The method of claim 74 wherein the support comprises a homopolymeric tail complementary to the homopolymeric tail of the probe.

76. A kit for detecting a target polynucleotide contained in a sample comprising:

(a) means for substantially separating the target polynucleotide from the sample prior to amplification of the target polynucleotide;

(b) means for amplifying *in vitro* the separated target polynucleotide; and

(c) means for detecting the presence of the amplified target polynucleotide as indicative of the presence of the target polynucleotide in the sample.

77. The detection kit of claim **76** wherein:

(a) the means for substantially separating the target polynucleotide from the sample include a first support and a probe that binds to both the first support and the target polynucleotide;

(b) the means for amplifying *in vitro* the separated target polynucleotide include a polymerase; and

(c) the means for detecting the presence of the amplified target polynucleotide include a detector probe.

78. The detection kit of claim **77** wherein the means for substantially separating the target polynucleotide from the sample includes a first support that binds to the target polynucleotide via a probe.

79. The detection kit of claim **78** wherein the means for substantially separating the target polynucleotide from the sample include a probe that first binds to the target polynucleotide by hybridizing to a specific sequence in the target polynucleotide, and then binds to the first support.

80. The detection kit of claim **79** wherein the means for amplifying the separated target polynucleotide include means for amplifying the target polynucleotide non-specifically with random primers.

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81. The detection kit of claim **79** wherein the means for amplifying the separated target polynucleotide include means for amplifying the target polynucleotide specifically with specially tailored primers.

82. The detection kit of claim **81** wherein the sample is a clinical sample.

REMARKS

Reissue Applications

In accordance with paragraphs 1 and 2 of the Office Action, the Patent Owner submitted on February 21, 2002, a Notice of Related Litigation, which addresses arguments made in litigation by the Protestor Gen-Probe concerning the patentability of the original claims of the patent for which reissue is sought. On February 21, 2002, the Patent Owner also submitted a Supplemental Information Disclosure Statement, which identifies references not already of record that Gen-Probe has relied upon in support of its arguments concerning the patentability of those claims.

Consent of Assignee and Offer to Surrender

In paragraph 6 of the Office Action, the application is objected to under 37 C.F.R. 1.172(a) on the grounds that the assignee has not established its ownership interest in the patent for which reissue is sought. On February 20, 2002, the Patent Owner submitted a Request for Recordation of Assignment of the '338 patent from Amoco Corporation to Vysis, Inc. to establish that Vysis, Inc. is the proper assignee. That Assignment has now been recorded at Reel 012407, Frame 200.

Paragraph 7 of the Office Action notes that the original patent, or a statement as to loss or inaccessibility of the original patent, must be received before the reissue application can be allowed, pursuant to 37 C.F.R. 1.178. The Patent Owner hereby submits the original patent to fulfill this requirement.

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Oath

At paragraphs 8 and 9 of the Office Action, claims 1-59 are rejected as being based on a defective reissue oath/declaration under 35 U.S.C. 251. The Office Action states that the reissue oath/declaration a) does not identify the citizenship of each inventor, b) does not identify the city and either state or foreign country of residence of each inventor, c) fails to identify at least one specific error which is relied on to support the reissue application, and d) fails to contain a statement that all errors that are being corrected in the reissue application up to the time of filing of the oath/declaration arose without any deceptive intention on the part of the Patent Owner.

The Patent Owner is submitting herewith a supplemental reissue declaration including the citizenship and residence information of each inventor, identifying at least one specific error relied on to support the reissue application, and the statement that all errors being corrected arose without any deceptive intention on the part of the Patent Owner. As detailed in the supplemental reissue declaration, the contentions of Gen-Probe in the related litigation have revealed the possibility of latent ambiguities in the language used in the original patent claims. For example, Gen-Probe has contended in related litigation that the order of the target capture and amplification steps and the nature of the amplification steps were not established by the original claim language. The selection of claim language that is vulnerable to ambiguous interpretation is an error correctable by reissue. *In re Altenpohl*, 183 U.S.P.Q. 38 (C.C.P.A. 1974). The Patent Owner, by this reissue application, seeks to correct this error and a number of others as reflected in this response.

More specifically, it is clear from the original specification that the claimed invention lay in employing techniques for the *in vitro* enzymatic amplification of nucleic acid sequence information from a target polynucleotide following specific capture of that target polynucleotide and its substantial separation from non-target polynucleotides, cellular debris, and impurities in the sample. *See* Office Action, discussion of Allowable Subject Matter, at pages 16-17. That the claims are so limited is now made clear by inclusion of the phrase "amplifying *in vitro* the

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separated target polynucleotide" in the claims. Gen-Probe contends that the original claims could be read as encompassing amplification prior to target capture, or amplification by other techniques, such as cloning. These contentions are now unambiguously foreclosed by the proffered amendments. Accordingly, the Patent Owner submits that the supplemental reissue declaration complies with 35 U.S.C. 251 and 37 C.F.R. 1.175 and thus the rejection of the claims has been obviated and should be withdrawn.

Claim Objections

In paragraph 10 of the Office Action, claims 35-37 are objected to because claim 35 recites "wherein the target polynucleotide is amplified a polymerase." The Patent Owner has mooted this objection by amending claim 35 to recite wherein the target polynucleotide is amplified *in vitro* "with a polymerase." The Patent Owner believes this amendment makes explicit what was already implicit in the claims and overcomes the objection to claim 35 and claims 36 and 37 directly or indirectly dependent thereon.

Specification

In paragraph 11 of the Office Action, the disclosure is objected to because of informalities in a Certificate of Correction granted on December 25, 2001. Specifically, the Office Action points out that amendments to the continuing information at col. 1, lines 4-18, are improper because no reference should be made to reissue in the continuing information as the face of the granted reissue will indicate that the patent is a reissue. The Office Action advises that the Patent Owner should delete from the specification the phrase "is a Reissue of Ser. No. 238,080, filed May 3, 1994, now U.S. Patent No. 5,750,338, which" by presenting that phrase in brackets. The Patent Owner has amended the specification as suggested by the Office Action to obviate this objection.

In addition, the Patent Owner proposes in this amendment two corrections to the "Related U.S. Application Data" on the face of the patent, and one correction to the continuing

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information at col. 1, lines 4-18 of the specification. First, the original Certificate of Correction in the '338 patent, as well as the Certificate granted on December 25, 2001, describe application Serial No. 238,080 as a "continuation" of application Serial No. 124,826 in both the Related U.S. Application Data and in the continuing information at col. 1 of the specification. While substantive rights do not turn on the word used to describe the relationship between the two applications, the Patent Owner believes that 238,080 should more properly be described as a "divisional" of 124,826 because application 238,080 contains some but not all of the disclosure of application 124,826. Second, the original Certificate of Correction in the '338 patent, as well as the Certificate granted on December 25, 2001, describes application Serial No. 644,967 as a "continuation-in-part" of application Serial No. 136,920 in the Related U.S. Application Data. Serial No. 644,967 was in fact a "continuation" of Serial No. 136,920 filed under 37 C.F.R. 1.60, as can be clearly seen from the application papers from the prosecution history enclosed herewith. The Patent Owner's amendments herein to the continuing information at col. 1, lines 4-18 and to the Related U.S. Application Data correct these informalities. Entry is respectfully requested.

Claim Rejections – 35 U.S.C. § 112

In paragraph 13 of the Office Action, claims 1-59 have been rejected under 35 U.S.C. 112, second paragraph, as indefinite because of the Patent Owner's proposed amendments adding dependent claims 41-59 that include the limitations "amplifying *in vitro*" and "*in vitro* amplification." The Office Action states that "the teachings of the specification and of the prior art, as well as Applicants' admissions on the record, indicate that the types of 'amplifying' that are intended to be encompassed by the instant claims are limited to *in vitro* types of amplification." Office Action, page 8. Thus, the Office Action states that "one of skill in the art cannot determine the metes and bounds of the claimed invention, and it is unclear as to how claims 41-59 are intended to be further limiting of the claims from which they depend." Office Action, page 8. The Patent Owner agrees with the Examiner that the terms "amplifying" and

"amplification" in the claims are properly construed to mean "*in vitro*" amplifying and "*in vitro*" amplification as construed by the Examiner. Nevertheless, as suggested by the Office Action, and in order to make explicit what was already implicit in the claims, the Patent Owner has amended the claims to expressly limit them to in vitro amplification. Support for this amendment can be found, for example, at col. 30, lines 15-40, Examples 4-7, and Figures 5-6. Accordingly, the Patent Owner respectfully submits that this rejection is obviated and should be withdrawn.

The Office Action rejects claims 1-19 and 41-53 as indefinite under 35 U.S.C. 112, second paragraph, because of the term "the target polynucleotide" in step c of claims 1, 7, and 19. The reference in step c of claims 1, 7, and 19 to "the target polynucleotide" is clearly intended to refer back to step b of those claims. As is expressly disclosed throughout the specification, the invention of the '338 patent is amplification of the target polynucleotide after the target polynucleotide has been substantially separated from the sample. See, for example, Examples 4-7, Figures 4-6, and col. 30, lines 15-40, of the '338 patent, and page 18, lines 10-13, of the Office Action. The Patent Owner submits that one of ordinary skill in the art would clearly understand from the teachings of the specification that the invention is directed to amplification after separation. To make explicit what was already implicit in the claims, the Patent Owner has amended the claims to expressly recite that amplification is of the separated target polynucleotide. Accordingly, this rejection is obviated and should be withdrawn.

The Office Action rejects claims 4-6, 10-12, 17-18, 29-33, 35-37, 39-53, and 56-59 as allegedly indefinite because of the recitation of the language "wherein the target polynucleotide is amplified." The Office Action states that it is "unclear as to whether applicants' intent is to further limit an 'amplifying' step (or steps) recited in a preceding claim, [or] whether applicants' intent is to require additional steps of amplification of 'target polynucleotide' at some other point in the claimed method (or at any time), etc." Office Action, page 9. The Patent Owner respectfully submits that these claims, because they use the language "wherein" rather than the language "further comprising," clearly limit the amplifying step in the claims from which they

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depend, and do not add an additional amplifying step. Accordingly, the Patent Owner submits that this rejection should be withdrawn.

The Office Action rejects claims 7-19, 38-40, 47-53, and 59 under 35 U.S.C. 112, second paragraph, for "failing to recite a final process step that clearly relates back to the claim preamble." Office Action, page 9. The Office Action states that the rejection "could be overcome by amending the claims to recite, e.g., "detecting the presence of the amplified target polynucleotide as indicative of the presence of the target polynucleotide in said sample." Office Action, page 10. The Patent Owner has followed the Examiner's suggestion and has amended claims 7, 13, 14, 16, 19, 28, and 38 to insert the Examiner's suggested language, which is implicit from the teachings of the specification relating to detection of an amplified target polynucleotide. Accordingly, this rejection is obviated with respect to these claims and claims 8-12, 15, 17, 18, 39, 40, 47-53, and 59 directly or indirectly dependent thereon.

The Office Action also rejects claims 13-16 under 35 U.S.C. 112, second paragraph, "because it is unclear as to how the limitations recited in claims 13-16 are intended to further limit the claims, particularly how the limitations are intended to relate to the objective of detecting a target polynucleotide." Office Action, page 10. The Patent Owner has amended claims 13, 14, and 16 to expressly recite that "the presence of the target polynucleotide in the sample is indicated by detection of said label [or labeled probe]." The Patent Owner believes that the newly added language makes explicit what was already implicit in the claims. Accordingly, the rejection of these claims is obviated, as well as the rejection of claim 15, dependent on claim 7, which has been similarly amended as set forth above.

The Office Action rejects claims 19 and 53 under 35 U.S.C. 112, second paragraph, because "it is unclear as to how the step of 'detecting the presence of the amplified target polynucleotide (step e) relates to or results from the 'contacting' of step d." Office Action, page 10. The Patent Owner has amended claim 19 to recite in step e "detecting the presence of the labeled probe as indicative of the presence of the target polynucleotide in said sample." The Patent Owner believes that the newly added language makes explicit what was already implicit

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in the claims. Accordingly, the Patent Owner believes that the rejection of claim 19 and claim 53 dependent thereon has been obviated.

The Office Action also rejects claims 20-23 and 54 under 35 U.S.C. 112, second paragraph, because there is insufficient antecedent basis for the limitation "the amplified target polynucleotide" in claim 20. The Patent Owner submits that the antecedent basis for "the amplified target polynucleotide" in claim 20 can be found in step b, which as amended recites "means for amplifying *in vitro* the separated target polynucleotide." Accordingly, the rejection of claim 20 and claims 21-23 and 54 dependent thereon should be withdrawn.

The Office Action also rejects claims 21-23 under 35 U.S.C. 112, second paragraph, stating that there is insufficient antecedent basis for the limitation "the means for binding that amplified target polynucleotide to a solid support" in claim 21. The Patent Owner has amended claim 21 to change "that amplified target polynucleotide" in claim 21, step c to "the amplified target polynucleotide." The Patent Owner believes this rejection of claim 21 and claims 22 and 23 directly or indirectly dependent thereon has been obviated.

The Office Action rejects claims 21-23 under 35 U.S.C. 112, second paragraph, stating that "it is unclear as to whether the recitation 'a detector probe for labeling . . .' is intended to be a further requirement of 'the means for binding' of c, whether applicants' intend for the claim to further inclusion [sic] of a detector probe in the kit, etc." Office Action, page 11. The Patent Owner has amended claim 21, step d, to recite "the means for labeling the amplified target polynucleotide include a detector probe," thus placing the claims in proper means plus function claim format. The Patent Owner believes the rejection of claim 21 and claims 22 and 23 directly or indirectly dependent thereon has been obviated.

The Office Action also rejects claims 22-23 under 35 U.S.C. 112, second paragraph, stating that there is insufficient antecedent basis for the limitation "the target" in claim 22, and it is unclear whether this is intended to refer back to "the target polynucleotide" or "the amplified target polynucleotide." The Patent Owner has amended claim 22 to recite "the target polynucleotide." The Patent Owner believes that this amendment makes explicit what was

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already implicit in the claims. Accordingly, the Patent Owner believes this rejection of claim 22 and claim 23 dependent thereon has been obviated.

The Office Action also rejects claims 27-33 and 56-57 under 35 U.S.C. 112, second paragraph, stating there is insufficient antecedent basis for the recitation "the target" in step a of claims 27 and 28 and it is unclear whether the recitation of "the target polynucleotide" in step g is intended to refer to "the target polynucleotide" recited in the claim preamble, "the target" recited in step a, or to a target polynucleotide that might be present in the medium of step f. Office Action, page 11. The Patent Owner has amended claims 27 and 28 to recite in step a of each "the target polynucleotide" and to recite in step g of each "the target polynucleotide present in the second medium." The Patent Owner believes that the newly added language makes explicit what was already implicit in the claims. Accordingly, the Patent Owner believes that this rejection of claims 27-28 and claims 29-33 and 56-57 directly or indirectly dependent thereon has been obviated.

Claim Rejections – 35 U.S.C. § 102

In paragraph 15 of the Office Action, claims 20-26 and 54-55 have been rejected under 35 U.S.C. 102(e) as allegedly anticipated by U.S. Patent No. 5,468,613 to Erlich et al. The Office Action states that Erlich et al. discloses primers, polymerization agents, and nucleoside triphosphates that constitute a "means for amplifying" a target polynucleotide as required by the Patent Owner's claims. The Office Action further states that Erlich et al. discloses a probe attached to a support, which constitutes both a "means for substantially separating" a target polynucleotide from a sample and a "means for binding" an amplified target polynucleotide to a solid support. The Office Action also states that Erlich et al. discloses labeled probes and labeled primers and/or nucleoside triphosphates, which constitute "means for labeling" amplified target polynucleotides. Regarding claims 21-23 and 26, the Office Action states that Erlich et al. discloses a probe affixed to a membrane, which constitutes a "capture probe which binds to" a "solid support" and to an "amplified target polynucleotide"/"target polynucleotide," as required

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by the claims. Regarding claims 21-23, the Office Action states that Erlich et al. discloses polymerization agents, including DNA polymerases. Regarding claims 54-55, the Office Action states that Erlich et al. discloses primers, polymerization agents, and nucleoside triphosphates that "provide for *in vitro* amplification . . . to produce a multitude of polynucleotide amplification products" as recited by the claims. Office Action, page 13. Without conceding the correctness of the Examiner's interpretation of Erlich et al., claims 20-26 have been amended to recite means for substantially separating the target polynucleotide from the sample prior to amplification of the target polynucleotide, and means for amplifying in vitro the separated target polynucleotide. Support for these amendments can be found, for example, at Examples 4-7, Figures 4-6, and col. 30, lines 15-40, of the '338 patent.

The Patent Owner submits that Erlich et al. does not teach "means for amplifying *in vitro* the separated target polynucleotide" as recited by the Patent Owner's claims 20-26 as amended. To the extent that Erlich et al. teaches "substantially separating" a target polynucleotide from a sample, the teaching is that such separation takes place after the polynucleotide is amplified, not before, as recited by the Patent Owner's claims 20-26. Accordingly, Erlich et al. does not anticipate claims 20-26 or claims 54-55 dependent thereon.

Claim Rejections – 35 U.S.C. § 103

In paragraph 18 of the Office Action, claims 20-26 and 54-55 are rejected under 35 U.S.C. 103(a) over Erlich et al. in view of U.S. Patent No. 5,273,882 to Snitman et al. The Office Action states that this rejection applies to the claims to the extent that they may be limited to kits comprising "retrievable" supports. Office Action, page 14. The Office Action states that Snitman et al. discloses kits comprising dispersible solid supports associated with capture probes and that those supports and capture probes may be used to capture hybridization complexes in solution. The Office Action submits that it would have been obvious to one or ordinary skill in the art at the time the invention was made to have modified the kits of Erlich et al. to have included the dispersible supports and associated capture probes taught by Snitman et al., or to

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have substituted the supports and probes of Snitman et al. for the probe affixed to a membrane disclosed by Erlich et al. Office Action, page 15.

Without conceding the correctness of the Examiner's analysis of the prior art, the Patent Owner submits that neither Erlich et al. nor Snitman et al. teaches or suggests, either alone or in combination, the invention of separating a target polynucleotide prior to amplification, as recited in the amended claims. To the extent that Erlich et al. and Snitman et al. suggest "substantially separating" a target polynucleotide from a sample, the teaching is that such separation takes place after the polynucleotide is amplified, not before, as recited by the Patent Owner's claims 20-26. As set forth in detail during procurement of the original patent and earlier in this reissue application, a significant benefit of the claimed invention is the substantial removal of inhibitors of the amplification process through target capture *prior* to amplification. Prior art processes such as Erlich et al., which suggest capturing amplified target *after* amplification, actually teach away from the presently claimed invention. In order to make explicit what the Patent Owner believes was implicit in the original kit claims to which this rejection has been applied, the claims have been amended to specify the presence of means for substantially separating the target polynucleotide *before* amplification. Accordingly, the invention of claims 20-26 is nonobvious over Erlich et al. in view of Snitman et al.

The Amendments to Claims 5, 11, 30, and 36

As set forth in greater detail in the accompanying Notice of Related Litigation, Gen-Probe has contended that the specification does not enable amplification of a target polynucleotide using Qβ replicase. The Patent Owner disagrees with that contention. Nonetheless, to render moot any contention that the claims must encompass the amplification of a target polynucleotide using Qβ replicase that might not work, the Patent Owner has amended claims 5, 11, 30, and 36 to eliminate reference to Qβ replicase. If, as Gen-Probe contends, Qβ replicase cannot be used for target amplification, then it is simply not within the scope of claims requiring successful target amplification.

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Newly-Presented Claims

Newly presented claims 64 and 65 are dependent on claim 1 and are, therefore, allowable, *inter alia*, for the reason that claim 1 is allowable. These claims recite the two alternative amplification techniques encompassed by the specification. Claim 64 calls for "non-specific" amplification with "random primers." "Non-specific" amplification is described at column 30, lines 31-33, and the use of "random primers" is described at column 31, lines 31-32. The use of "specially tailored primers" of the sort that result in specific amplification, as set forth in claim 65, is supported in the specification by reference to "specially tailored primers" at column 30, line 38, by the residuum of the disclosed genus of "amplification" processes left by exclusion of the described species of "non-specific" amplification (*see, e.g., In re Johnson*, 194 U.S.P.Q. 187 (C.C.P.A. 1977) (description of genus and species describes genus minus species)), as recognized by the Examiner in the outstanding Office Action (paragraph bridging pages 16-17, page 22, and page 28). The claim language in claims 64-65 is repeated but depending from other claims in claims 66-69, 71-72, and 80-81.

Newly presented claim 70 depends from claim 7 and is allowable, *inter alia*, for the reason that claim 7 is allowable. Claim 70 specifically recites the option that the capture probe binds first to the target polynucleotide and then to the solid support. This option is described in detail in each of Examples 4-7 (*see, e.g.*, column 30, lines 48-58) and illustrated in each of Figures 4, 5, and 6. Similar claim language appears in added dependent claim 79.

Claim 73 is ultimately dependent on claim 7 and is, therefore, allowable, *inter alia*, for the reasons applicable to claim 7. Claim 73 specifies that the sample is a "clinical sample" and is supported by the disclosure at, *inter alia*, column 5, line 64. This language also appears in dependent claim 82.

Dependent claims 74 and 75 are ultimately dependent on claim 7 and, therefore, are also allowable. Claim 74 specifies that the probe contains both a nucleotide sequence complementary to the target polynucleotide and a homopolymeric tail. Claim 75 specifies that the support has a

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homopolymeric tail complementary to the tail on the probe. Both claims 74 and 75 are supported, *inter alia*, by Figures 4-6.

Claims 76-82 define a kit for detecting a target polynucleotide that includes reagents in addition to those specified for the amplification kit of original claims 24 and 25 and are, therefore, narrower than those kit claims. The added reagents are those required for detection of the amplified target polynucleotide and are supported, *inter alia*, in the same manner as the similar language in original claims 20 and 21.

THE PROTEST OF FEBRUARY 15, 2002

The Patent Owner also wishes to respond briefly to the Protest filed on February 15, 2002 ("Protest II"). Protest II does not identify the real party in interest, but the similarity of the issues raised in Protest II to the arguments previously made by Gen-Probe suggests that the protest may have been submitted in active concert with Gen-Probe. In any event, the remarks in the Patent Owner's Notice of Related Litigation, submitted on February 21, 2002, address virtually all of the points raised in Protest II. The following additional comments are offered to facilitate review of the Protest.

Protest II urges that the combination of the publications by Pollet et al. (1967) and Feix et al. (1968) renders the claimed invention obvious. Whatever suggestion might be gleaned from a combination of the laborious purification of Qβ RNA minus strand and the synthesis of infectious viral RNA from the minus strand, the 20 years that passed between the publications of these papers and the filing of the application for the claimed invention in 1987 demonstrates that no one in the art looked at Pollet and Feix as providing any reasonable expectation of success, even to those with experience in the Qβ field. These early experiments certainly did not suggest to Gen-Probe, the original Protestor, that the combination of target capture followed by amplification was obvious. Indeed, as detailed in the Patent Owner's response to Gen-Probe's protest, Gen-Probe's web site touts as "new" the notion of purification of target polynucleotide molecules before amplification:

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> The major limitation of current nucleic acid amplification assays is the sample processing step which is usually complex, time consuming, and often does not eliminate interfering substances that can inhibit the amplification reaction. Target Capture is a new sample-preparation technology, which partially purifies the target nucleic acid before the amplification process.

Moreover, the combination of Pollet and Feix cannot provide all the elements of the claimed invention. As concisely set forth in the Office Action section on Allowable Subject Matter, the capture step yields targets of known identity due to the specificity imparted by target capture. *See* page 18, section 18, first paragraph. There is no such teaching in Pollet and, thus, the combination of references cannot render the claimed invention obvious.

Protest II then relies on Chu et al. (U.S. Patent No. 4,957,858) as providing additional motivation to combine separation of target polynucleotide with amplification, but Chu only discusses amplification of the probe, not amplification of the target. Indeed, Chu is entitled "Replicative RNA Reporter Systems," and the specification only describes amplification of these RNA reporter systems. The RNA probes are joined to a "biopolymer analyte" and then the RNA probes are "replicated *in vitro* by an RNA-directed RNA polymerase" to assay for the biopolymer analyte. *See* Summary of the Invention, columns 3 and 4. Moreover, Chu teaches away from amplifying the target polynucleotide by expressly disclosing amplification of only the probe even when the probe is attached to a nucleic acid. *See* col. 3, line 64 to col. 4, line 42.

Thereafter, Protest II recites a series of signal amplification publications (Dattagupta et al., U.S. Patent Nos. 4,724,202, 4,737,454; Schneider et al. U.S. Patent No. 4,882,269; and Stuart et al., U.S. Patent No. 4,*732*,847) as sources of additional motivation. As with Chu, any suggestion to amplify the signal simply teaches away from a method based on the amplification of the separated target polynucleotide.

Protest II then offers Feix et al. as an anticipatory reference. As noted above, however, there is no teaching of a specific capture step.

Protest II also contends that the reissue oath is defective, but this point is moot in view of the submission of the Supplemental Reissue Oath, as discussed above.

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Finally, Protest II argues that the reissue oath is defective because Scott Decker contributed "to reduction to practice of the claimed invention" and thus should be added as an inventor and a new oath executed by all the inventors. This argument relies on an erroneous statement of the law. Inventorship is determined by conception, not by reduction to practice. Only inventors can conceive of the invention, but any one can reduce the invention to practice. MPEP 2137.01; *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460, 45 U.S.P.Q.2d 1545, 1548 (Fed. Cir. 1998); *Mergenthaler v. Scudder*, 11 App. D.C. 264, 1897 CD 724 (C.A.D.C. 1897). Thus, even if Dr. Decker had reduced to practice the combination of target capture and PCR, which the Patent Owner does not concede, he would not be an inventor. Of course, the argument that combining target capture and PCR was a reduction to practice of the claimed invention is clearly inconsistent with any argument that the claimed invention does not encompass specific amplification.

CONCLUSION

For the foregoing reasons, the Patent Owner respectfully submits that the claims are in condition for allowance and earnestly requests prompt notification to this effect.

If there are any fees due in connection with the filing of this Amendment not already accounted for, please charge the fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

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Dated: March 8, 2002
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Appendix showing amendments to claims added in the Preliminary Amendment

42. (Amended) The amplification method of claim [**41**] 1 wherein the amplification is linear or exponential.

44. (Amended) The amplification method of claim [**41**] 1 wherein the target polynucleotide is amplified with a polymerase and at least one oligonucleotide primer.

46. (Amended) The amplification method of claim [**41**] 1 wherein the target polynucleotide is amplified with more than one polymerase.

48. (Amended) The detection method of claim [**47**] 7 wherein the amplification is linear or exponential.

50. (Amended) The detection method of claim [**47**] 7 wherein the target polynucleotide is amplified with a polymerase and at least one oligonucleotide primer.

52. (Amended) The detection method of claim [**47**] 7 wherein the target polynucleotide is amplified with more than one polymerase.

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